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TITLE: Prostate Cancer Clinical Consortium Clinical Research Site: Targeted Therapies

PRINCIPAL INVESTIGATOR: David Nanus

CONTRACTING ORGANIZATION: Weill Medical College of Cornell University
New York, NY 10065

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14. ABSTRACT

The Weill Cornell Medical College Prostate Cancer Research Program (WCMC-PCRP) is a Clinical Research Site of the Prostate Cancer Clinical Trials Consortium (PCCTC). The purpose of the research is to lead and participle in Consortium therapeutic and correlative science research protocols. Specifically, our aims are to impact prostate cancer care and outcomes through the development and study of novel targeted therapeutics, discovery of mechanisms of therapy resistance/sensitivity, identification of new therapeutic targets through high quality genomic analyses, providing access to the highest quality PC tissue specimens, and development of molecular imaging techniques with direct relevance to targeted therapies. Our overarching goal is to more effectively bring novel agents and new biomarker driven trials directly to patients

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The Weill Cornell Medical College Prostate Cancer Research Program (WCMC-PCRP) is a Clinical Research Site of the Prostate Cancer Clinical Trials Consortium (PCCTC). The purpose of the research is to lead and participle in Consortium therapeutic and correlative science research protocols. Specifically, our aims are to impact prostate cancer care and outcomes through the development and study of novel targeted therapeutics, discovery of mechanisms of therapy resistance/sensitivity, identification of new therapeutic targets through high quality genomic analyses, providing access to the highest quality PC tissue specimens, and development of molecular imaging techniques with direct relevance to targeted therapies. Our overarching goal is to more effectively bring novel agents and new biomarker driven trials directly to patients

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

aurora kinase A, clinical trials, circulating tumor cells, monoclonal antibody, neuroendocrine prostate cancer, next-generation sequencing, prostate cancer, Prostate Cancer Clinical Trials Consortium, prostate specific membrane antigen, translational research program,

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the USAMRAA Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

SOW Major Task 1: Adhere to performance metrics defined by Coordinating Center
SOW Major Task 2: Full participation in the consortium as a member of the Clinical Consortium Committee/Scientific Oversight Committee
SOW Major Task 3: Regulatory review, Clinical trial startup
SOW Major Task 4: Propose clinical trials to Consortium
SOW Major Task 5: Interim data analysis
SOW Major Task 6: Open other Consortium sponsored Clinical Trials at WCMC
SOW Major Task 7: Clinical trial performance
SOW Major Task 8: Investigator analysis, reporting of initial data
SOW Major Task 9: Analysis and reporting of final data

What was accomplished under these goals?

SOW Major Task 1: Adhere to performance metrics defined by Coordinating Center

Subtask 1. Accrue at least 25 patients per year to PCCTC trials: Sixteen (16) patients have enrolled to the 5 currently active PCCTC protocols in this reporting period. Four of the 5 studies were open less than six months.

- PCCTC LOI# c11-092 ("AbiCure") – activation date: 2/5/2015 – **3** enrolled (+1 additional screen failure)

- PCCTC LOI# c12-108 ("AbiCabazi") – activation date: 3/26/2015 – **1** enrolled
- PCCTC LOI# c13-124 ("RadPRO") – activation date: 6/22/2015 – **5** enrolled
- PCCTC LOI# c14-144 ("PCF Challenge") – activation date: 5/12/2015 - **1** enrolled
- PCCTC LOI# c12-105 ("MLN8237") – **6** enrolled at Weill Cornell Medical College (WCMC) for this reporting period. In addition, 32 subjects have been enrolled to this study at collaborating outside sites (+7 screen failures), whose research samples have were sent to WCMC for correlative studies.

PCCTC LOI# c12-105: 32 subjects enrolled at collaborating outside sites had research samples sent to WCMC for correlative studies.

PCCTC LOI# c14-144: 16 samples for CTC analysis (14 baseline samples and two progression samples).

PCCTC LOI# 12-107: This trial (TAXYNERGY) is closed to accrual but analysis of data is ongoing (see below). This trial was open at WCMC prior to the start of the grant, and 8 patients were enrolled to it.

Subtask 2. Accrue at least 5% of patients from disproportionately affected populations per year

Two of 16 enrolled patients were Hispanic (6.25%)

Subtask 3. Propose ≥ 2 clinical trials per year or 6 trials over 3 years for consideration by the consortium, which may include biomarker studies: We are co-investigators on a PCF Challenge Award with Duke open this past year, and participated in its design (PCCTC LOI# c14-144). Circulating tumor cells are sent to WCMC for analysis from other centers (Johns Hopkins, Duke and MSKCC). We also proposed (together with the University of Oregon) and will soon open "A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination with Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone". This trial will open first quarter 2016. In addition, a WCMC-initiated multicenter consortium study with funding support from Janssen Biotech, Inc. is in development and will be offered through PCCTC when finalized. The LOI has been submitted to the PCCTC and is pending distribution.

Subtask 4. Participate as a Clinical Research Site in >6 trials initiated by other sites: We have opened 4 trials to date initiated by other sites, including one in which we are co-investigators on a PCF Challenge Award. Other protocols are in various stages of completion and/or start up.

SOW Major Task 2: Full participation in the consortium as a member of the Clinical Consortium Committee/Scientific Oversight Committee

Subtask 1. Participate in ≥1 PCCTC committee:

Dr. Nanus participates in the Scientific Oversight Committee

Subtask 2. Attend all face-to-face meetings of the PCCTC: Dr. Nanus, Dr. Tagawa and/or Dr. Beltran attended all face-to-face meetings of the PCCTC.

Subtask 3. Participate in scheduled consortium conference calls: Dr. Nanus and/or Dr. Tagawa have participated in all PCCTC scheduled consortium conference calls. Dr. Nanus will present on the conference call for Weill Cornell in December 2015.

Subtask 4. Participate in review meetings/evaluation by the External Advisory Board (EAB): No EAB meetings have yet occurred.

Subtask 5. Compliance with the operations manual of the Consortium: We have been compliant.

SOW Major Task 3: Regulatory review, Clinical trial startup.

Subtasks 1 thru 4 have each been completed (Submission of protocols for scientific (WCMC Protocol Review Committee) and WCMC Institutional Review Board (WCMC Clinical and Translational Science Center review if indicated); Completion of contractual agreements between Coordinating Center and WCMC; Clinical trial approval at WCMC; and Site initiation visits). Four new (4) consortium trials have been open at WCMC in the past year, with additional trials in various stages of regulatory review.

SOW Major Task 4: Propose clinical trials to Consortium

Subtask 1. Propose new therapeutic trial to Coordinating Center and other Consortium sites: See above (Major Task 1, Subtask 3).

Subtasks 2- thru 7. Subtasks 2 thru 7 are partially accomplished and ongoing as specifically related to each WCMC initiated protocol (Submission of protocol for scientific review; start up at additional sites; clinical trial initiation at WCMC and other collaborating sites; Screen, enroll, and treat subjects; ongoing communication with study sites; Ongoing communication with IRB, DSMB, FDA).

SOW Major Task 5: Interim data analysis

This milestone has not yet been reached. Two PCCTC trials (c12-105 and 12-107) led or co-led by WCMC have or are completing accrual with analysis planned for Fall/Winter 2015.

SOW Major Task 6: Open other Consortium sponsored Clinical Trials at WCMC

See above in Major Task 1 for details.

SOW Major Task 7: Clinical trial performance

See above in Major Task 1 for details.

SOW Major Task 8: Investigator analysis, reporting of initial data

Subtask 1. Verification of data

This milestone has not yet been reached. See Major Task 5.

Subtask 2. Analysis of initial data

1. Demographic data This milestone has not yet been reached – analyses planned for Fall/Winter 2015

2. Toxicity data This milestone has not yet been reached – analyses planned for Fall/Winter 2015

3. Response data This milestone has not yet been reached– analyses planned for Fall/Winter 2015

4. Biological correlate data

Analysis of circulating tumor cells for androgen receptor localization at screening and baseline has been performed on CTC samples from the TAXYNERGY study and reported at national/international meetings.

Subtask 3. Reporting of initial data

Two biological correlative data abstracts have reported on circulating tumor cell analysis from the TAXYNERGY trial: A) Baseline analysis of circulating tumor cell (CTC) enumeration and androgen receptor (AR) localization in men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY. J Clin Oncol 2015; 33 (15 Suppl) Abst 5031; and B) Screening and baseline analysis of circulating tumor cell (CTC) counts and androgen receptor (AR) localization with clinical characteristics of men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY. European Journal of Cancer 2015; 51 (suppl 3), S498 (abst 2563).

SOW Major Task 9: Analysis and reporting of final data

This milestone has not yet been reached.

What opportunities for training and professional development has the project provided?

Dr. Beltran has had the opportunity to be involved in a multi-institutional clinical trial (PCCTC LOI# c12-105) as PI, communicating with other sites. She will also be involved in the analysis of response and correlative studies data.

Dr. Tagawa had the opportunity to attend the European Cancer Congress 2015.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue to recruit to currently open consortium studies, as well as open other clinical trials being offered through the consortium. Given that this is the first year of the grant, studies have not been open for the duration of the full year. We expect increased enrollment to consortium studies in the upcoming year. We also currently have a WCMC-initiated study in development, which will be offered to other sites in the consortium in the upcoming year.

4. IMPACT:

Nothing to Report

5. CHANGES/PROBLEMS:

Nothing to Report

6. PRODUCTS:

Two abstracts were presented (one at the 2015 annual meeting for the American Society of Clinical Oncology, and one at the European Cancer Congress 2015).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Personnel	Role	Percent Effort
David Nanus	Principal Investigator	10%
Mark Rubin	Co-Investigator	3%
Scott Tagawa	Co-Investigator	3%
Himisha Beltran	Co-Investigator	3%
Irene Karpenko	Clinical Research Coordinator	45%
Lauren Emmerich	Research Nurse	44.13%
Gillian Hodes	Data Coordinator	45.5%

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

David Nanus:

The NIH grant U54 CA143876, "Center on the Microenvironment and Metastasis," on which Dr. Nanus acted as Project Leader, ended on 7/31/15.

Scott Tagawa:

Dr. Tagawa has requested an additional no-cost extension on his DOD grant W81XWH-09-1-059, which was scheduled to end 8/16/15. This request is currently pending.

Mark Rubin:

Dr. Rubin was awarded a Prostate Cancer Foundation Challenge Award ($170,000 direct costs per year) for "Targeting Genomic Instability in SPOP Mutant Prostate Cancer" and a New York State Department of Health Grant for "Prostate Cancer Research" ($75,000 direct costs). In

addition, Dr. Rubin executed the sponsored research agreements, “Identification of Neuroendocrine Prostate Cancer (NEPC)-Specific Antigens and Antibodies” with Janssen Pharmaceutical Company ($640,288 direct costs) and “Development of Novel Therapeutics for Treatment of Neuroendocrine Prostate Cancer” with Eli Lilly & Company ($127,776 direct costs) during this reporting period.

Dr. Rubin also serves as Co-Investigator on Dr. Beltran’s Alliance for Clinical Trials in Oncology Foundation’s Alliance Scholar Award ($40,000 direct costs per year) for “Impact of therapy on modulation of neuroendocrine-associated gene expression in patients with high risk, localized prostate cancer treated with neoadjuvant docetaxel and androgen deprivation therapy”, and on the NIH grant P50 CA186786, “SPORE in Prostate Cancer” led by Dr. Arul Chinnaiyan at the University of Michigan ($1,412,572 direct costs, year one).

Dr. Rubin had the DoD grant W81XWH-11-1-0410 and the NIH grants R01 CA152057 and U01 CA152738 (Mercola) end in the past year.

Himisha Beltran:

Dr. Beltran received the 2014 Prostate Cancer Foundation Challenge Award ($352,215 direct costs for year one) for her project “Early Detection of Neuroendocrine Prostate Cancer Transformation Using Circulating Genomic Signatures”. She was also awarded the Alliance for Clinical Trials in Oncology Foundation’s Alliance Scholar Award ($40,000 direct costs per year) for “Impact of therapy on modulation of neuroendocrine-associated gene expression in patients with high risk, localized prostate cancer treated with neoadjuvant docetaxel and androgen deprivation therapy”. Finally, Dr. Beltran also executed a sponsored research agreement with Eli Lilly and Company ($58,997 direct costs) on “Characterizing Molecular Determinants of Response to LY2835219 in Advanced Prostate Cancer”.

In addition, Dr. Beltran serves as Co-Investigator on the newly executed sponsored research agreements, “Identification of Neuroendocrine Prostate Cancer (NEPC)-Specific Antigens and Antibodies” with Janssen Pharmaceutical Company ($640,288 direct costs, led by Dr. Rubin) and “Development of Novel Therapeutics for Treatment of Neuroendocrine Prostate Cancer” with Eli Lilly & Company ($127,776 direct costs, led by Dr. Rubin).

During the reporting period, Dr. Beltran’s Prostate Cancer Foundation Young Investigator Award, “The Molecular Basis of Neuroendocrine Prostate Cancer,” ended.

What other organizations were involved as partners?

This grant is for the PCCTC consortium, which is a collaboration between all consortium sites.

8. SPECIAL REPORTING REQUIREMENTS:

None

9. APPENDICES:

Copies of abstracts (see Major Task 8; subtask 3).

Abstract #146500

Baseline analysis of circulating tumor cell (CTC) enumeration and androgen receptor (AR) localization in men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY.

Scott T. Tagawa, Giuseppe Galletti, Emmanuel S. Antonarakis, Shinsuke Tasaki, Ada Gjyrezi, Daniel Worroll, Luigi Portella, Brian J. Kirby, John Stewart, Atef Zaher, Fred Saad, Marie Vanhuyse, Shalu Suri, Timothy B Lannin, Conor Gruber, Erica Pratt, Guru Sonpavde, Mario A. Eisenberger, David M. Nanus, Paraskevi Giannakakou; Weill Medical College of Cornell University, New York, NY; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Sanofi, Laval, QC; University of Montreal, Montreal, QC; Medical Oncology, Montréal General Hospital, Montréal, QC; Cornell University, Ithaca, NY; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL

Abstract Text:

Background: Microtubule-targeted therapy with taxanes is the only chemo with survival benefit in advanced PC. Emerging molecular evidence suggests sensitivity/resistance to taxanes may relate to the ability of microtubules to inhibit AR nuclear trafficking. CTCs represent a real-time biomarker for molecular testing including taxane-induced microtubule stabilization and AR nuclear localization. **Methods:** TAXYNERGY is an international, multicenter phase 2 trial in progressive, chemo-naïve mCRPC men randomized (2:1) to docetaxel or cabazitaxel. Pre-treatment CTCs were enriched from 1 ml blood via a prostate-specific microfluidic device, enumerated, and analyzed by multiplex confocal microscopy for AR cellular localization. Nuclear AR % was calculated by integrating fluorescence intensity in the total cell and nuclear area. Bivariate correlations and multiple regressions examined associations between baseline characteristics and % nuclear AR or CTC count. **Results:** 63 men were randomized (median age 70 [range 53–84], median PSA 89 [2.4–1558], 24 [38%] previously received a CYP17 inhibitor and/or enzalutamide, 17 [27%] had visceral metastases). Of 59 with evaluable samples, CTCs were detected in 52 (88%), median 10 CTCs/mL of blood [0–542]. 638 CTCs were analyzed for AR localization with a mean 61.2% [30–85] nuclear AR per subject. Higher baseline LDH, pain assessments, and ECOG performance status were associated with higher CTC counts; LDH ($p = 0.013$) and analgesic scores ($p = 0.036$) remained significant on multivariate analysis. Visceral metastases were associated with a lower fraction of nuclear AR, remaining significant on multivariate analysis ($p = 0.045$). **Conclusions:** Nearly 90% of men with progressive chemo-naïve mCRPC have detectable CTCs available for molecular analysis using this platform, with higher CTC counts associated with adverse prognostic variables. Lower percent of nuclear AR was associated with visceral metastases, suggesting progressive visceral CRPC may be less AR-driven. The predictive value of these biomarkers for taxane response is being evaluated.

Title: Baseline analysis of circulating tumor cell (CTC) enumeration and androgen

receptor (AR) localization in men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY.
Submitter's E-mail Address:danielle.lindley@meditechmedia.com
Is this a late-breaking abstract?No
Is this abstract a clinical trial?Yes
Is this clinical trial registered?Yes
Registry Name: Clinicaltrials.gov
Registration Number:NCT01718353
Research Funding Source: Pharmaceutical/Biotech Company
Research Funding Source Name: Sanofi
Would like to be considered for a Merit Award: No
Presentation Format: Regular

Trial Type: Phase II
Research Category: Clinical
Continued Trial Accrual: No
Received Grant funding: No
Relevant to geriatric oncology: No
Sponsor: Scott T. Tagawa, MD

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Conclusions: In this EAP, pts receiving Abi/Enza with Ra-223 had a longer OS compared with Ra-223 alone, suggesting that this combination may be more effective than Ra-223 alone. The safety profile was comparable between pts with or without concomitant Abi/Enza with no new toxicities reported. These findings require further confirmation and are currently being assessed in a randomized, phase III clinical trial.

Conflict of interest: *Advisory Board: Joe O'Sullivan holds consulting/advisory roles with Bayer Janssen, and Astellas. Silke Gillessen holds consulting/advisory roles with Dendreon, Sanofi, Pfizer, Millenium, Amgen, Bayer, Janssen, Astellas, Orion, and Curevac. Axel Heidenreich holds consulting/advisory roles with Astellas, Bayer, Sanofi and Dendreon. Daniel Heinrich holds consulting/advisory roles with Astellas, Bayer and Amgen. Jeremy Gratt holds consulting/advisory roles with Bayer. Kurt Miller holds consulting/advisory roles with Bayer, BMS, Dendreon, Ferring, Janssen, Merck, Pfizer and Roche. Sten Nilsson holds consulting/advisory roles with Bayer. Fred Saad holds consulting/advisory roles with Bayer, Janssen, Astellas and Amgen. Tucci Marcello holds consulting/advisory roles with Atellas and Bayer. Manfred Wirth holds consulting/advisory roles with Janssen, Takeda, Merck, Bayer, Dendreon and Ferring. Joan Carles holds consulting/advisory roles with Bayer, Astellas, Janssen, Pfizer and Sanofi. Corporate-sponsored Research: Joe O'Sullivan has received funding for research from Bayer. Silke Gillessen has received funding for research from Millenium. Axel Heidenreich has received funding for research from Atellas and Sanofi. Kurt Miller has received funding for research from Novartis. Fred Saad has received funding for research (paid to his institute) from Bayer. Manfred Wirth has received funding for research (paid to his institute) from Apogepha, Sanofi-Aventis, Ferring and Takeda. Other Substantive Relationships: Joe O'Sullivan has received honoraria from Bayer, Astellas and Janssen, and speaker's bureau fees from Bayer, and Janssen. Silke Gillessen has received patents and royalties from Proteomedix. Axel Heidenreich has received honoraria and speaker's bureau fees from Astellas, Bayer Dendreon, Janssen, Ipsen, Sanofi and Pfizer. Daniel Heinrich has received honoraria from Janssen-Cilag, Astellas and Bayer, and has had travel, accommodation and/or other expenses paid for by Bayer. Jérémy Lévy is an employee of BIOP and provided statistical support funded by Bayer. Kurt Miller has received speaker's bureau fees from Janssen and Novartis, and has has had travel, accommodation and/or other expenses paid for by Janssen and Roche. Sten Nilsson has received honoraria, speaker's bureau fees, and has had travel, accommodation and/or other expenses paid for by Bayer. Fred Saad has received honoraria from Bayer, Janssen, Astellas and Amgen. Manfred Wirth has received honoraria from Apogepha, Astellas, Orion, and Sanofi-Aventis. Joan Carles has received speaker's bureau fees from Janssen and Astellas.*

2562 POSTER

Chromogranin A and Enolase levels in serum as prognostic factors in castration prostate cancer resistant

N. Sala Gonzalez[1], M. Buxo[2], J. Mora[3], P. Maroto[4], J. Palou[5], S. Esquena[5], G. Sancho[6], A. Barnadas[4]. *[1]Ico-Girona, Oncology, Girona, Spain; [2]Hospital Josep Trueta, Girona Biomedical Research Institute, Girona, Spain; [3]Hospital Santa Creu i Sant Pau, Biochemical Service, Barcelona, Spain; [4]Hospital Santa Creu i Sant Pau, Medical Oncology, Barcelona, Spain; [5]Fundacio Puigvert, Urology, Barcelona, Spain; [6]Hospital Santa Creu i Sant Pau, Oncology Radiotherapy, Barcelona, Spain*

Background: The natural evolution of prostate cancer is to a situation of hormone resistance. One possible hypothesis is presence of neuroendocrine differentiation of prostate cancer. Chromogranin A (CGA) and Enolase are serum markers associated with neuroendocrine tumors.

Purpose: Analyze neuroendocrine markers, CGA and enolase as prognostic factors in patients with prostate cancer resistant to castration (CPRC)

Material and Methods: We analyzed prospectively the CGA and enolase in serum of 75 patients with CPRC. We set a high value of serum CGA if it was >100 ug/L and enolase >16 ug/L. CGA-E was defined as having both, only one or none of two biomarkers altered. Survival was defined as time between castration resistant diagnosis and date of death or last control. Survival analysis was performed using Kaplan–Meier method and differences between survival curves were analyzed using log-rank test. Relation between categorical variables was evaluated by chi-square test. A P-value less than 0.05 was considered statistically significant.

Results: Mean age was 68.5 years (42−88). Median follow-up of was 16 months. 41 patients had bone metastasis, 23 patients had lymph node and 11 had visceral metastatic disease. At baseline, 17 patients were enolase-negative (23%), and 57 (76%) were enolase-positive. 39 patients were CGA-negative (52%), and 36 (48%) were CGA-positive. Univariate analysis revealed that both markers (CGA, enolase and CGA-E) were significantly associated to poor prognosis. Patients with higher levels of CGA or enolase (median, CGA: 27 months; enolase: 9 months) had lower survival than those with normal values (median, CGA: 35 months; enolase: 35 months; $p < 0.001$ and $p = 0.02$, respectively). Also, patients with higher values in both markers had worse prognosis than patients with one or neither (median:7 months; 30 months and NR, respectively; $p < 0.001$).

There was a significant relationship between CGA-E and response to treatment ($p = 0.007$), showing a moderate association (Cramer's V =0.414). Patients with one of two markers altered show lower response rate (8.3%) than those with none markers altered (48.1%) or both markers altered (42.9%).

We did not find relation between hormone-sensitive time and chromogranin and/or enolase elevated.

Conclusion: The prospective analysis conducted suggests that alterations in serum Chromogranin and Enolase could be prognostic and predictive factor in patients with prostate cancer resistant to castration

No conflict of interest.

2563 POSTER

Screening and baseline analysis of circulating tumor cell (CTC) counts and androgen receptor (AR) localization with clinical characteristics of men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY

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Background: Taxanes are the only class of chemo with a survival benefit in prostate cancer. Emerging molecular evidence suggests sensitivity/resistance to taxanes may relate to the ability of microtubules to inhibit AR nuclear trafficking. Analysis of CTCs represent a real-time biomarker of taxane drug–target engagement to examine microtubule stabilization and AR nuclear localization.

Methods: TAXYNERGY is an international, multicenter phase 2 trial in progressive, chemo-naïve mCRPC men randomized (2:1) to docetaxel or cabazitaxel with a potential switch to the alternative taxane after 4 cycles if PSA did not decline by at least 30%. Two sets of CTCs were collected (screening and baseline) with no intervening treatment to prospectively assess precision of the primary biomarkers. CTCs were enriched from 1 mL blood via a prostate-specific microfluidic device, enumerated, and analyzed by multiplex confocal microscopy for AR cellular localization. Nuclear AR % was calculated by integrating fluorescence intensity in the total cell and nuclear area. Bivariate correlations and multiple regressions examined associations between baseline characteristics and CTC count.

Results: 63 men were randomized (median age 70, median PSA 89 [range 2.4–1558], 38% previously received a CYP17 inhibitor and/or enzalutamide, 27% with visceral metastases). Analysis of 39 paired pre-treatment samples obtained a median of 6 days (1−20) apart revealed good concordance with a difference of only 0.27% in median percent nuclear AR localization at screening vs baseline. Because of good concordance, screening data was substituted for the 9 patients with unevaluable CTCs at baseline. Of 63 with available baseline or screening samples, CTCs were evaluable in 62 (98.4%). Higher CTC counts were associated with higher baseline LDH and pain assessments; analgesic score ($p = 0.0364$) and present pain intensity score ($p = 0.0031$) remained significant on multivariate analysis. As expected in men with progressive CRPC, the majority of the 738 CTCs had nuclear AR localization (mean 62.9%) with observed CTC heterogeneity within patients (range 31−91% within individual subjects).

Conclusions: Using this platform, greater than 98% of men with progressive chemo-naïve mCRPC have detectable CTCs available for molecular analysis, with higher CTC counts associated with adverse prognostic variables. The majority of men at progression from prior AR-directed therapy had nuclear AR localization, though intra-subject CTCs demonstrated heterogeneity. The predictive value of these biomarkers for taxane response is of potential value and is being evaluated as the co-primary endpoint of the study. TAXYNERGY (NCT01718353) is a Sanofi-sponsored study.

Conflict of interest: *Ownership: John Stewart owns Sanofi stock. Advisory Board: Fred Saad has had membership on an advisory board for Sanofi.*

Scott North has received honoraria from Sanofi for an advisory board meeting. Corporate-sponsored Research: Scott Tagawa has received research funding from Sanofi, Astellas/Medivation, Janssen, Dendreon, Amgen, Lilly, Progenics, Newlink and BMS. Emmanuel S. Antonarakis has received research funding from Janssen, Johnson & Johnson, Sanofi, Dendreon, Exelixis, Genentech, Novartis and Tokai. Fred Saad, Conor Gruber and Mario Eisenberger have received research funding from Sanofi. Timothy Lannin's research laboratory has received funding from Sanofi. Scott North and John Stewart have been involved in corporate-sponsored research. Other Substantive Relationships: Scott Tagawa has acted in a consultancy/advisory role for Sanofi, Astellas/Medivation, Janssen and Bayer. Emmanuel S. Antonarakis has acted in a consultancy/advisory role for Janssen, Astellas, Sanofi, Dendreon, Essa and Medivation, and is also a co-inventor of a technology that has been licensed to Tokai. John Stewart is an employee of Sanofi. Atef Zaher is a contracted employee of Sanofi. Fred Saad has received honoraria from Sanofi, and has acted in a consultancy/advisory role for Sanofi. Mario Eisenberger has acted in a consultancy/advisory role for Sanofi. The following authors have no conflicts of interest to disclose: G. Galletti, S. Tasaki, A. Gjyrezi, D. Worroll, L. Portella, B.J. Kirby, M. Vanhuyse, S. Suri, E. Pratt, D.M. Nanus, P. Giannakakou.

2564 POSTER

The influence of prior novel androgen receptor targeted therapy on the efficacy of cabazitaxel in men with metastatic castration-resistant prostate cancer

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Background: The treatment armamentarium for metastatic castration-resistant prostate cancer (mCRPC) has expanded with the introduction of several new therapies. In this treatment continuum, it is unclear whether the efficacy of cabazitaxel is affected by prior novel androgen receptor targeted therapies (ART) such as abiraterone acetate and enzalutamide. In this study, we aimed to investigate the influence of prior ART on the efficacy of cabazitaxel in men with mCRPC.
Materials and Methods: Data from an ongoing prospective, multicenter, randomized phase II trial (CABARESC) were used comprising 114 men with mCRPC treated with cabazitaxel (25 mg/m^2 every 3-weeks) plus prednisone in the post-docetaxel setting. The primary endpoints of the current analysis were PSA response ($\geqslant$50%), and overall survival (OS). Univariate and multivariable analyses were conducted to investigate the influence of prior ART on the efficacy of cabazitaxel as defined by OS and PSA response rates.
Results: From the 114 patients included in this analysis, 44 men received prior ART and 70 men did not receive prior ART before treatment with cabazitaxel. PSA response rates ($\geqslant$50%) while on cabazitaxel treatment were similar in patients with and without prior ART (34% versus 40%, respectively, P = 0.53). Likewise, median OS was not significantly different between men with and without prior ART (9.8 months versus 10.6 months, respectively, logrank P = 0.65). In multivariable analysis, the only variables significantly associated with OS were performance score, alkaline phosphatase and albumin at baseline.
Conclusion: Our study showed that prior treatment with ART may not influence the efficacy of cabazitaxel in men with mCRPC. With emerging evidence of cross-resistance between the currently available therapies in mCRPC, cabazitaxel provides a good treatment option irrespective of prior treatment.
Conflict of interest: *Advisory Board: Andries Bergman and Ronald de Wit have served on the advisory board of Sanofi. Corporate-sponsored Research: Ronald de Wit and Robert van Soest have received research funding from Sanofi. Other Substantive Relationships: Ronald de Wit has received consultancy and speaker honoraria from Sanofi, Janssen, and Millenium. Robert van Soest has received honoraria from Sanofi.*

2565 POSTER

QoLiTime: Quality-of-Life (QoL) analysis of patients with metastatic castration resistant prostate cancer (mCRPC) treated with cabazitaxel in daily clinical practice

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Background: Cabazitaxel (Caba) in combination with Prednis(ol)one is approved for 2nd-line treatment of mCRPC for Docetaxel pre-treated patients. Chemotherapy may have a negative impact on patient's QoL inspite of treatment benefits. Thus, QoL data are important from both physicians' and patients' perspective.
Methods: Patients with mCRPC receiving Caba were included in the non-interventional study QoLiTime. The cancer specific questionnaire EORTC QLQ C30 was handed out to patients at baseline and each cycle. The primary endpoint was the correlation of QoL with biochemical response (PSA decrease >50%) fter 4 cycles (C4) of Caba. Secondary endpoints included further QoL analyses as well as TTP, OS and safety of Caba under daily practice conditions.
Results: The total population consists of 527 patients, 406 received 4 cycles of Caba, 266 of those had PSA measurements at BL and C4 and 238 completed the EORTC QLQ 30 at BL and C4. Median age was 72 years with good performance status (ECOG 0:36%; ECOG 1:54%). No significant change in QoL was observed between BL and C4, independent of PSA response. Significant and clinically relevant changes for QLQ scales between BL and C4 were seen in the total population for physical and role functioning (−5.21, $p < 0.0001$, and −8.79, $p < 0.0001$), fatigue (6.49, $p = 0.0003$), dyspnoea (6.36, $p = 0.004$) and diarrhoea (9.16, $p < 0.0001$). Other scales did not vary significantly from BL to C4. Changes for physical functioning and pain corresponded with PSA response, with a pain decrease (−7.61) for patients with a PSA decrease >50% and a pain increase (3.44) for patients with a PSA decrease <50%. The TTP in this setting was 8.3 months, OS was 16.8 months. No new safety signals were seen.
Conclusions: This study is the largest prospective analysis of QoL to date in patients receiving Cabacitaxel for mCRPC. Symptom increases were seen in typical areas of chemo toxicity such as fatigue and diarrhoea, but QoL was maintained during the 12-week observation period. Change of pain from BL to C4 differs significantly between patients with a PSA response >50% and a PSA response <50%. Caba was safe and effective in this clinical practice setting.
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No conflict of interest.

2566 POSTER

Cabazitaxel for metastatic castration-resistant prostate cancer (mCRPC) real data in real life

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Background: Cabazitaxel, a novel taxane developed to overcome Docetaxel resistance showed an overall survival improvement after Docetaxel in mCRPC (Tropic Study). The overall survival in mCRPC patients is clearly increasing in the last five years due to new treatments approved. We perform a retrospective analysis of the clinical outcome with Cabazitaxel in the community setting in two major hospitals in Madrid.
Material and Methods: Patients (Pts) with mCRPC after Docetaxel faillure (follow-up >6 months) were included. Pts received Cabazitaxel 25mg/m^2 every 3 weeks + prophylactic GSCF until progressive disease or unacceptable toxicity. Radiological assesment were defined according PCWG2 criteria and RECIST 1.1.
Results: 64 pts were identified, 47 met all criteria. Median age was 69 yo (47−83), ECOG 0−1: 70%. Bone metastases: 85% (80% with >10 bone metastases), visceral disease: 20% and lymph node metastases: 34%. Gleason score $\geqslant$8: 61%. 98% pts received Docetaxel as first line treatment with a median of 8 cycles (4−12). 57% of pts received Cabazitaxel as 2nd line treatment with a median of 8 cycles (3−19), 70% showed >50% decrease in PSA, 22% had partial response, 7% progressive disease and 70% obtained stable disease. Most frequent Grade >3 adverse events were: G3−4 neutropenia: 14%, febrile neutropenia 15%, asthenia 44%, anaemia 8%, diarrhoea 4%, the median PFS was 7 months 95% CI (4.2–